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SUPLEMENTASI TRI® E MEMODULASI EKSPEKSI GEN DAN PROTEIN
PADA SEL MONONUKLEAR DARAH PERIFERI DAN PLASMA
DI KALANGAN INDIVIDU BERBEZA UMUR



TESIS YANG DIKEMUKAKAN UNTUK MEMPEROLEH IJAZAH SARJANA
SAINS PERUBATAN (BIOKIMIA)



FAKULTI PERUBATAN
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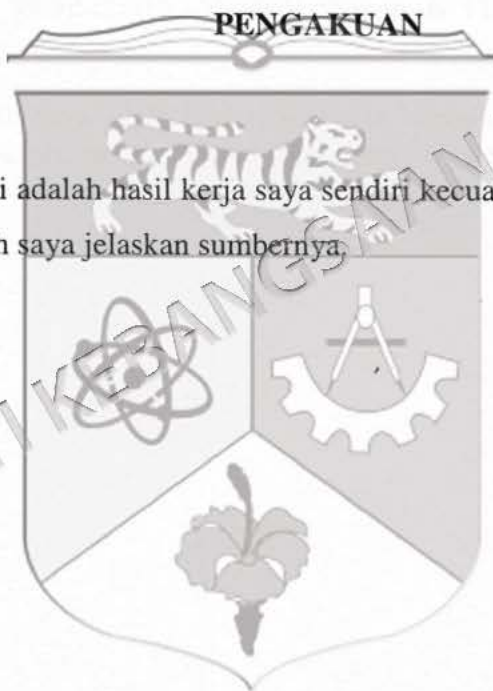
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PENGAKUAN

Saya akui karya ini adalah hasil kerja saya sendiri kecuali nukilan dan ringkasan yang setiap satunya telah saya jelaskan sumbernya.

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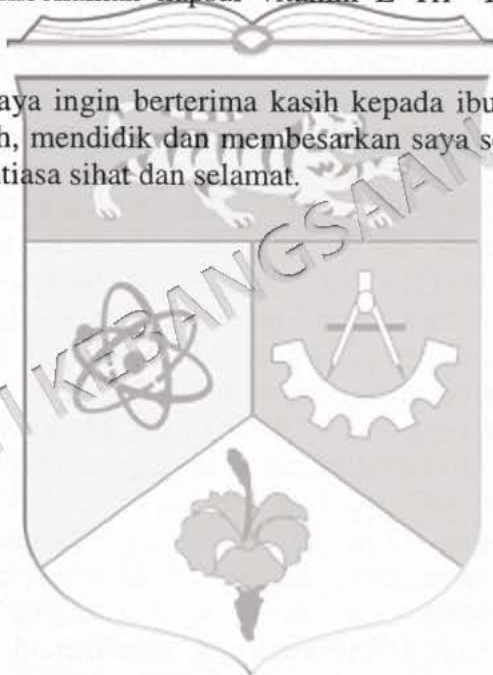


PENGHARGAAN

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ABSTRAK

Vitamin E jenis tokotrienol dilaporkan mempunyai sifat hipokolesterolemik, anti-kanser dan perlindungan saraf yang berbeza daripada tokoferol dalam kajian *in vitro* dan *ex vivo*. Kajian mencadangkan tokotrienol berfungsi melalui kawalan ekspresi gen dan protein yang mungkin memodulasi kejadian penyakit. Namun, kajian suplementasi tokotrienol di kalangan manusia pada tahap molekular kurang dilakukan terutamanya pada manusia berbanding dengan tokoferol. Matlamat kajian ini adalah mengkaji kesan suplementasi Tri[®] E tokotrienol pada ekspresi gen sel mononuklear darah periferi (PBMC) dan protein plasma manusia. Seramai 14 orang subjek wanita dibahagikan kepada dua kumpulan: 6 subjek muda umur 32±2 (3 penerima plasebo & 3 Tri[®] E) and 8 subjek lebih tua umur 52±2 (4 penerima plasebo & 4 Tri[®] E) pada dos 150 mg sehari. Darah berpuasa (15 ml) diambil pada 0, 3 dan 6 bulan. mRNA diekstrak daripada PBMC dan asai mikroatur dilakukan dengan GeneChip Human Gene 1.0 ST diikuti validasi melalui qRT-PCR. Analisis statistik dengan $p < 0.05$, FDR < 0.05 dan ganda perubahan > 1.5 dikira signifikan. Hasil kajian menunjukkan 102 gen (32↑ dan 70↓) dan 282 gen (78↑ dan 204↓) mengalami perubahan ekspresi pada kumpulan subjek muda selepas 3 dan 6 bulan pengambilan Tri[®] E masing-masing. Gen yang mengalami penurunan signifikan di kalangan subjek muda terlibat dalam fungsi penekatan kitaran sel (GADD45A, GADD45B, ATM), apoptosis (TNF, PLEKHF1, BAK1), inflamasi (ICAM1, IER3, MIF), angiogenesis (S100A4), dan kolesterol homeostasis (DHCR7, SC5DL). Pada kumpulan subjek berumur, suplementasi Tri[®] E menyebabkan 15 gen (4↑ dan 11↓) dan 523 gen (45↑ dan 478↓) mengalami perubahan ekspresi selepas 3 dan 6 bulan. Gen yang mengalami penurunan termasuk sitokin (IL1A, CXCL2, CCL3, CCL4), apoptosis (TNF, PLEKHF1, BAK1, DDIT4), inflamasi (ICAM1, IER3, MIF), angiogenesis (S100A4, S100A9, S100A11), dan homeostasis kolesterol (SC5DL, DHCR7). Gen pengikat DNA (LRRFIP1) dan regulasi G protein (RGS18) mengalami peningkatan signifikan pada subjek muda dan berumur suplementasi Tri[®] E. Protein plasma telah dikaji menggunakan 2D-GE dan MALDI-TOF TOF menunjukkan 3↑ dan 6 (5↑ dan 1↓) protein mengalami perubahan ekspresi pada kumpulan subjek muda berbanding dengan 6↑ dan 8 (7↑ dan 1↓) protein pada subjek berumur selepas 3 dan 6 bulan suplementasi masing-masing. Protein dikenalpasti berkaitan homeostasis kolesterol (APO A1, APO E), inflamasi akut (CRP), respon imun (FHR1, FHR2), dan perencat protease (CBPN). Protein pengangkutan kolesterol APO A1 dan APO E didapati mengalami peningkatan manakala protein petanda inflamasi CRP menurun pada kedua-dua kumpulan. Penentuan vitamin E dengan HPLC menunjukkan peningkatan ($p < 0.05$) pada kedua-dua kumpulan subjek suplementasi Tri[®] E manakala tiada perubahan paras vitamin E pada plasebo. Kesimpulan, suplementasi Tri[®] E memberi kesan perlindungan melalui perubahan ekspresi gen dan protein yang berkaitan anti-apoptosis, anti-inflamasi dan homeostasis kolesterol di mana tempoh dan umur didapati mempengaruhi respon terhadap suplementasi tokotrienol.

TRI[®] E SUPPLEMENTATION MODULATES GENE AND PROTEIN EXPRESSION OF PERIPHERAL BLOOD MONONUCLEAR CELL AND PLASMA IN DIFFERENT AGED INDIVIDUALS

ABSTRACT

Tocotrienol forms of vitamin E are reported to possess hypocholesterolemic, anti-cancer and neuroprotective properties different from tocopherol in *in vitro* and *ex vivo* studies. Research on tocotrienol has suggested the modulation of gene and protein expression that may regulate disease development. But, human supplementation studies using tocotrienol at the molecular level are limited in comparison to tocopherol. The aim of this study is to determine the effects of Tri[®] E tocotrienol supplementation on gene expression in human peripheral blood mononuclear cells (PBMC) and plasma proteins. Fourteen female subjects were divided into two groups: 6 younger subjects aged 32 ± 2 (3 received placebo & 3 Tri[®] E) and 8 older subjects aged 52 ± 2 (4 received placebo & 4 Tri[®] E) at a dose of 150 mg/day. Fasting blood (15ml) was taken at 0, 3 and 6 months. mRNA was extracted from PBMC and microarray assay conducted using GeneChip Human Gene 1.0 ST followed by validation using qRT-PCR. Statistical analysis were set at $p < 0.05$, FDR < 0.05 and fold change > 1.5 for significance. Results obtained showed that Tri[®] E supplementation altered 102 genes (32 $\uparrow$ and 70 $\downarrow$) and 282 genes (78 $\uparrow$ and 204 $\downarrow$) for younger subjects after 3 and 6 month supplementation respectively. Significantly down-regulated genes were involved in cell cycle arrest (GADD45A, GADD45B, ATM), apoptosis (TNF, PLEKHF1, BAK1), inflammation (ICAM1, ICAM2, IER3, MIF), angiogenesis (S100A4), signal transduction (TGF β 1, SOCS1, SOCS3) and cholesterol homeostasis (DHCR7, SC5DL). For the older subjects, Tri[®] E caused 15 genes (4 $\uparrow$ and 11 $\downarrow$) and 523 genes (45 $\uparrow$ and 578 $\downarrow$) differentially expressed after 3 and 6 month respectively. The genes that were down-regulated included cytokine (IL1A, CXCL2, CXCL3, CCL4), apoptosis (TNF, PLEKHF1, BAK1, DDIT4), inflammation (ICAM1, ICAM3, IER3, MIF), angiogenesis (S100A4, S100A9, S100A11), signal transduction (TGF β 1, AKT1, SOCS3) and cholesterol homeostasis (SC5DL, DHCR7). DNA binding gene (LRRFIP1) and regulator of G protein (RGS18) were significantly up-regulated in both younger and older subjects with Tri[®] E. Plasma proteins were studied using 2D-GE and MALDI TOF-TOF showed 3 $\uparrow$ and 6 (5 $\uparrow$ and 1 $\downarrow$) proteins were affected in younger subjects as compared to 6 $\uparrow$ and 8 (7 $\uparrow$ and 1 $\downarrow$) proteins in the older subjects after 3 and 6 months supplementation respectively. The proteins identified were related to cholesterol homeostasis (APO A1, APO E), acute inflammation (CRP), immune response (FHR1, FHR2), and protease inhibitor (CBPN). Cholesterol transport protein APO A1 and APO E were found to be up-regulated while inflammation marker CRP was down-regulated in both groups. Vitamin E determination by HPLC showed that total vitamin E increased ($p < 0.05$) in both younger and older subjects taking Tri[®] E while vitamin E level in the placebo remained unchanged. Conclusion, Tri[®] E supplementation provides beneficial effect through differential expression of genes and protein related to anti-apoptosis, anti-inflammation and cholesterol homeostasis where duration and age were found to affect response towards tocotrienol supplementation.

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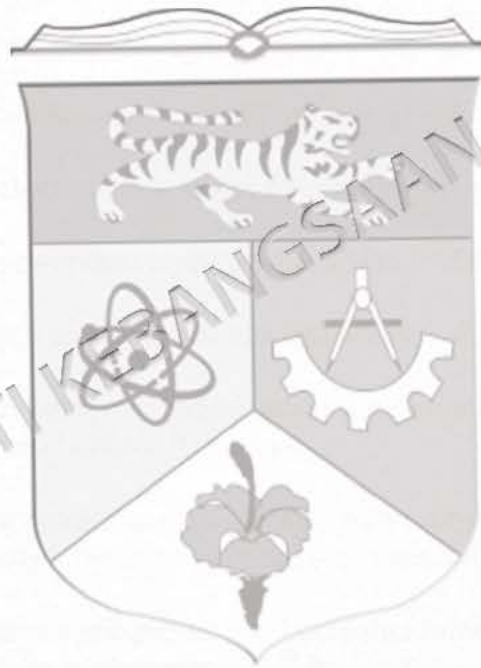
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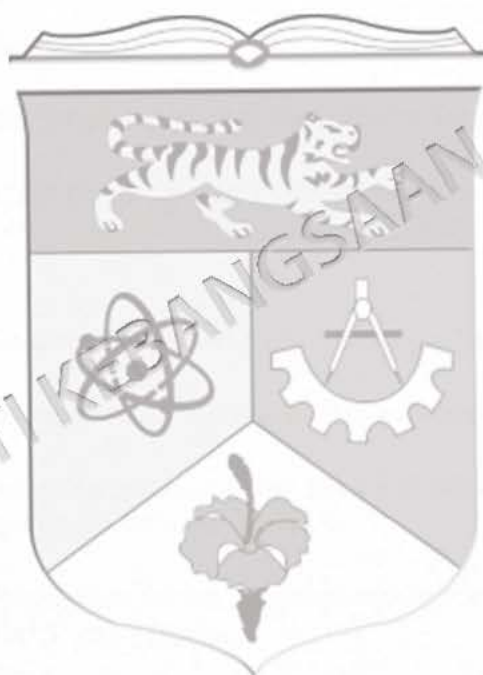


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SENARAI SINGKATAN/ SIMBOL

8-OH-DG	<i>8-hydroxy-2'-deoxyguanosine</i>
ABCA	<i>ATP-binding cassette subfamily A</i>
ACN	<i>Acetonitrile</i>
AIF	<i>Apoptosis inducing factor</i>
AKT	<i>v-akt murine thymoma viral oncogene homolog</i>
AMBP	<i>Alpha-1-microglobulin/bikunin precursor</i>
ANOVA	<i>Analysis of variance</i>
APAF	<i>Apoptosis-protease-activating factor</i>
ATBC	<i>Alpha-tocopherol, beta-carotene cancer prevention</i>
ATP	<i>Adenosina trifosfat</i>
AUC	<i>Area under curve</i>
APC	<i>Antigen presenting cell</i>
BAX	<i>Bcl-2-associated X protein</i>
BMI	<i>Body mass index</i>
BSA	<i>Bovine serum albumin</i>
CBPN	<i>Carboxypeptidase N catalytic chain</i>
CCND1	<i>Cyclin-D1</i>
cDNA	<i>Complementary DNA</i>
CEBP	<i>CCAAT/enhancer-binding protein</i>
CHAOS	<i>Cambridge heart antioxidant study</i>
CHAPS	<i>3-[(3-cholamidopropyl)dimethylammonio]-1-propanesulfonate</i>
DICS	<i>Death-inducing signalling complex</i>
DNA	<i>Asid deoksibonukleik</i>
dsDNA	<i>DNA bebenang ganda dua</i>
DTH	<i>Delayed-type hypersensitivity</i>
DTT	<i>Dithiothreitol</i>
ELISA	<i>Enzyme-linked immunosorbent assay</i>
FADD	<i>Fas associated death domain</i>

FC	<i>Fold change</i>
FDR	<i>False discovery rate</i>
FEME	<i>Full examination and microscopy examination</i>
GISSI	<i>Gruppo italo per lo Studio della Soprawivenza nell' infarto miocardico</i>
GO	<i>Gene ontology</i>
GSEA	<i>Gene set enrichment analysis</i>
HCl	Asid hidroklorik
HDL	Lipoprotein ketumpatan tinggi
HMG-CoA	3-hidroksil-3-metil-glutaryl koenzim A
HPLC	<i>High performance liquid chromatography</i>
HOPE	<i>Heart outcomes prevention evaluation</i>
HRP	<i>Horseradish peroxidase</i>
IAP	<i>Inhibitors of apoptosis</i>
ICAM	Intraselular adhesi molekul
IEF	<i>Isoelectric focusing</i>
IFN	Interferon
IL	Interleukin
IU	<i>International Unit</i>
JAK	<i>Janus protein kinase</i>
JNK	<i>c-Jun amino terminal kinase</i>
JUN	Onkogen daripada virus avian osteosarcoma
kDa	kilo Dalton
LCAT	<i>Lecithin-cholesterol acyltransferase</i>
LC-MS	<i>Liquid chromatography- mass spectrometry</i>
LDL	Lipoprotein ketumpatan rendah
LPS	Lipopolisakarida
MALDI	<i>Matrix assisted laser desorption/ionization</i>
MAPK	<i>Mitogen-activated protein kinase</i>
MCP1	<i>Monocyte chemotactic protein-1</i>
mTOR	<i>Mammalian target of rapamycin</i>
NaHCO ₃	Natrium bikarbonat
NaOH	Natrium hidroksida

NCBI	<i>National center for biotechnology information</i>
NF- κ B	Nuklear factor- κ B
oxLDL	<i>Oxidized low density lipoprotein</i>
PAGE	Poliakrilamid gel elektroforesis
PBS	Penimbal fosfat salin
PBMC	Sel mononuklear darah periferi
PCR	Reaksi berantai polimerase
PGE ₂	Prostaglandin E2
PHS	<i>Physician Health Study</i>
PI3K	<i>Phosphoinositide 3-kinase</i>
PMF	<i>Peptide mass fingerprinting</i>
RCT	<i>Reverse cholesterol transport</i>
REV	<i>Relative expression volume</i>
RIN	<i>RNA integrity number</i>
RNS	Spesis nitrogen reaktif
ROS	Spesis oksigen reaktif
SCE	<i>Sister chromatid exchange</i>
SDS	Natrium dodeksil sulfat
SELDI	<i>Surface enhanced laser desorption/ionization</i>
SOCS	<i>Suppressor of cytokine signalling</i>
TBARS	<i>Thiobarbituric acid reactive substances</i>
TBST	<i>Tris-buffered saline tween-20</i>
TEMED	N,N,N',N' - tetrametiletilenediamin
TFA	Asid trifluoroasetik
TGF	<i>Transforming growth factor</i>
TNF	<i>tumor necrosis factor</i>
TRADD	<i>TNF type 1-associated DEATH domain</i>
TRF	Fraksi kaya tokotrienol
TTP	<i>Tocopherol transfer protein</i>
UFLC	<i>Ultra-fast liquid chromatography</i>
WHS	<i>Women Health Study</i>

BAB I

PENDAHULUAN

1.1 PENGENALAN

Golden Age of Nutrition bermula pada tahun 1912 (Carpenter 2003) telah membuka peluang kepada aplikasi nutrien vitamin dalam mengubati, mencegah, dan memelihara kesihatan daripada penyakit. Mengikut laporan *Demand and Opportunities in Asia Pacific Nutritional Supplements Industry*, suplementasi mikronutrien merupakan perniagaan industri yang nilainya berbillion-billion ringgit di seluruh dunia pada tahun 2010 (Market Research 2011). Pertumbuhan industri yang pantas ini adalah hasil berikutan kerjasama para saintis, doktor dan pakar pemakanan. Bilangan pengguna yang mengambil suplementasi terutamanya vitamin dan mineral meningkat dengan pertumbuhan pantas di negara ASIA seperti Hong Kong, India, China, Singapura, Malaysia dan Jepun. Kebanyakan negara ASIA mengalami proses transformasi ekonomi, corak hidup, perbelanjaan akibat fenomena pambandaran telah melahirkan golongan pengguna peka kesihatan.

Secara umumnya, vitamin boleh dibahagikan kepada dua kategori iaitu vitamin berjenis semula jadi dan sintetik. Vitamin bersifat antioksidan terdiri daripada vitamin A, C dan E. Vitamin E merupakan jenis vitamin larut lemak utama yang terlibat dalam kaskad penghalangan rantai peroksidasi (Burton et al. 1982; Herrera & Barbas 2001). Fungsi asas vitamin E adalah memelihara integriti plasma membran yang kaya dengan asid lemak poli tak tepu (PUFA) daripada berlakunya lipid peroksidasi oleh radikal bebas (Traber & Atkinson 2007). Proses auto-oksidasi yang berterusan dapat merosakkan struktur sel membran dan seterusnya fungsi tisu akan terjejas (Rimbach et al. 2002). Jadi, vitamin E yang bersifat larut lemak ini dikatakan berkesan dalam

menghalang dan menyingkirkan radikal bebas yang bertindak pada sel membran (Brigelius-Flohe & Traber 1999).

Antara sumber radikal bebas oksigen (ROS) termasuklah ion-ion superoksida ($O_2^{\bullet-}$), hidrogen peroksida (H_2O_2) dan radikal hidroksil ($OH^{\bullet}$) terhasil secara *in vivo* daripada proses respirasi aerobik, fagositosis dan metabolik sitokrom P-450 (Rimbach et al. 2002). Mitokondria telah dikenalpasti sebagai organel utama penghasilan tenaga ATP dan juga ROS seperti $O_2^{\bullet-}$ sebagai produk sampingan (Remmen & Richardson 2001). Impak penghasilan ROS ini akan menyebabkan kerosakan oksidatif pada mitokondria jika tidak dineutralkan serta-merta (Harman 1972). Sebagai akibatnya, lebih banyak ROS akan terhasil dan bertindak pada mitokondria lain, sitosol, protein dan komponen nukleus yang akhirnya akan menjurus kepada proses apoptosis (Sastre et al. 2000).

Radikal bebas nitrogen (RNS) seperti peroksinitril ($ONOO^{\bullet}$) terhasil daripada tindak balas nitril oksida ($NO^{\bullet}$) dan anion superoksida ($O_2^{\bullet-}$) secara spontan tanpa bantuan sebarang enzim. Dalam keadaan pro-inflamasi, penghasilan $O_2^{\bullet-}$ dan $NO^{\bullet}$ secara serentak dalam kadar 10 kali ganda pada setiap molekul akan meningkatkan pembentukan $ONOO^{\bullet}$ sebanyak 100 kali ganda (Pacher et al. 2007). Paras $ONOO^{\bullet}$ yang tinggi akan menyebabkan berlakunya proses oksidasi, kemusnahan komponen selular, gangguan isyarat sel, induksi kematian sel melalui apoptosis dan nekrosis (Virag et al. 2003).

Radikal bebas juga boleh dihasilkan oleh sel sistem imun yang terlibat dalam aktiviti sitotoksik seperti sel makrofaj (Fuentes 2002). Namun, pembebasan ROS dan RNS yang berlebihan daripada kemampuan peneutralan oleh enzim antioksidan dalam sel imun boleh menyumbang kepada kemusnahan tisu dan seterusnya menjejaskan respon imun (Calder & Newholme 1993). Kesan radikal bebas ini adalah kritikal terutamanya terhadap sel darah putih seperti sel limfosit T dan B dalam sistem imun manusia. Fungsi sistem imun adalah terpengaruh oleh keseimbangan antioksidan dan oksidan di mana paras antioksidan memainkan peranan penting dalam melindungi sel imun daripada tekanan oksidatif (Knight 2000). Antara penyakit yang telah dikenalpasti berpunca daripada radikal bebas ialah arteriosklerosis (Madamanchi et al.

2005; Singh & Jialal 2006), kanser (Olinski et al. 2003; Reuter et al. 2010), Alzheimer (Stewart & Heales 2003; Shibata & Kobayashi 2008), dan Parkinson (Jenner et al. 2003; Henchcliffe & Beal 2008).

Beberapa kajian menunjukkan α -tokoferol mempunyai sifat anti-inflamasi (Mabile et al. 1999; Jialal et al. 2001; Singh et al. 2005), anti-kanser (Sigounas et al. 1997; Azizi et al. 2003), dan fungsi perlindungan saraf (Morris et al. 2005). Ada pula penyelidik melaporkan α -tokoferol tiada kesan kebaikan pada perkembangan kognitif (Kang et al. 2006) dan α -tokotrienol sahaja yang dapat melindungi saraf (Khanna et al. 2006; Sen et al. 2006). Walau bagaimanapun, suplementasi α -tokoferol di kalangan subjek manusia secara kohort pada 4 kajian percubaan klinikal (ATBC, CHAOS, GISSI, HOPE) pula menunjukkan keputusan yang konflik. Kajian ATBC melaporkan kesan negatif α -tokoferol pada peningkatan kes strok dibandingkan subjek plasebo (Rapola et al. 1994) manakala CHAOS pula menunjukkan penurunan signifikan sebanyak 77% kes penginfarkan miokardium dibandingkan dengan subjek kontrol (Stephens et al. 1996). Kajian GISSI dan HOPE menunjukkan tiada kesan positif suplementasi α -tokoferol pada aktiviti kardiovaskular. Perbezaan keputusan daripada kajian percubaan klinikal ini mungkin disebabkan oleh status kesihatan subjek, kedudukan geografi, tahap penyakit, dos, tempoh dan jenis sumber vitamin E (Brigelius-Flohe et al. 2002).

Kajian suplementasi vitamin E terdahulu sering menumpu pada ahli isomer α -tokoferol. Keadaan ini disebabkan paras α -tokoferol berada dalam kepekatan yang tinggi di dalam badan dibandingkan dengan kumpulan isomer tokotrienol yang lain. Tokotrienol adalah banyak terkandung pada sumber buah kelapa sawit yang terdiri daripada α -, γ -, δ -tokotrienol serta sedikit α -tokoferol yang dikenali sebagai fraksi kaya tokotrienol (TRF) (Sundram & Gapor 1992). Tokotrienol dikatakan mempunyai aktiviti perlindungan saraf (Osakada et al. 2004; Sen et al. 2009; Khanna et al. 2010), anti-tumor (Shah & Sylvester 2005; Miyazawa et al. 2009; Wali et al. 2009) kebolehan menurunkan paras kolesterol darah (Qureshi et al. 2002; Ajuluchukwu et al. 2007) dan aktiviti antioksidan (Maniam et al. 2008; Lee et al. 2009) yang jauh lebih baik daripada isomer tokoferol sahaja. Tokotrienol diiktiraf sebagai vitamin E pada kurun ke-21 berdasarkan kepelbagaian fungsi yang ditunjukkan dan ciri istimewa

rantai isoprenoid tak tepu yang dimilikinya (Packer 1991). Walau bagaimanapun, penyelidikan berkaitan dengan fungsi dan aktiviti tokotrienol dalam manusia adalah sangat sedikit berbanding dengan isomer tokoferol (Sen et al. 2006).

Kajian yang dijalankan oleh Meydani et al (1997) menunjukkan kesan positif vitamin E terhadap gerak balas imun dengan dos sebanyak 200 mg sehari selama 4 bulan setengah di kalangan warga tua sihat berumur 65 tahun ke atas. Antara indeks respon imun yang diukur adalah melalui peningkatan DTH, proliferasi sel limfosit T, IL2 dan penurunan produk lipid peroksidasi PGE₂. Hasil kajian suplementasi oleh Chin et al (2008) mendapati bahawa Tri[®] E berkeupayaan menurunkan petanda tekanan oksidatif melalui asai komet, SCE dan 8-OH-DG pada kumpulan subjek manusia berumur 50 tahun ke atas. Kumpulan kajian subjek ini dibahagikan kepada dua kumpulan iaitu subjek muda (<50 tahun) dan berumur (>50 tahun). Beliau mencadangkan suplementasi Tri[®] E mendatangkan manfaat dan respon yang ketara pada kumpulan subjek berumur dibandingkan subjek muda selama 6 bulan suplementasi pada dos 160 mg sehari.

Dalam ulasan Ordovas dan Mooser (2004), nutrien dan gen interaksi sering berkait rapat dengan kajian ekspresi gen pada sel dan tisu khususnya sel darah putih dalam kajian melibatkan penyelidikan manusia. Kini, kesan suplementasi vitamin pada peringkat gen, protein ataupun metabolik dapat dikaji berikutan perkembangan teknologi biologi molekul yang merangkumi bidang genomik, transkriptomik, proteomik, dan metabolomik (Kusmann et al. 2006). Suplementasi α -tokoferol dilaporkan merencat ekspresi gen kolagen $\alpha 1$ (Chojkier et al. 1998). Ekspresi enzim kolagenase berkorelasi dengan peningkatan umur pada sel fibroblas manusia dan ekspresi mRNA boleh diturunkan dengan rawatan α -tokoferol (Ricciarelli et al. 1999). Ekspresi reseptor SR-A dan CD36 juga dapat diturunkan oleh α -tokoferol tetapi tiada kesan bagi β -tokoferol pada sel otot (Ricciarelli et al. 2000) dan sel monosit ataupun makrofaj (Teupser et al. 1999; Devaraj et al., 2001). Pengaitan ekspresi CD36 pada proses arterosklerosis telah dibuktikan di mana gangguan ekspresi gen CD36 dapat menghalang pembentukan lesi aterosklerosis pada organisma tikus (Febbraio et al., 2000). α -Tokoferol juga dilaporkan menurunkan ekspresi gen yang terlibat dalam sintesis VCAM1 pada sel makrofaj, CD62L pada sel makrofaj (Sabat et al. 2001) dan

molekul adhesi diinduksi sitokin pada sel vaskular endotelium manusia (Zapolska et al. 2000).

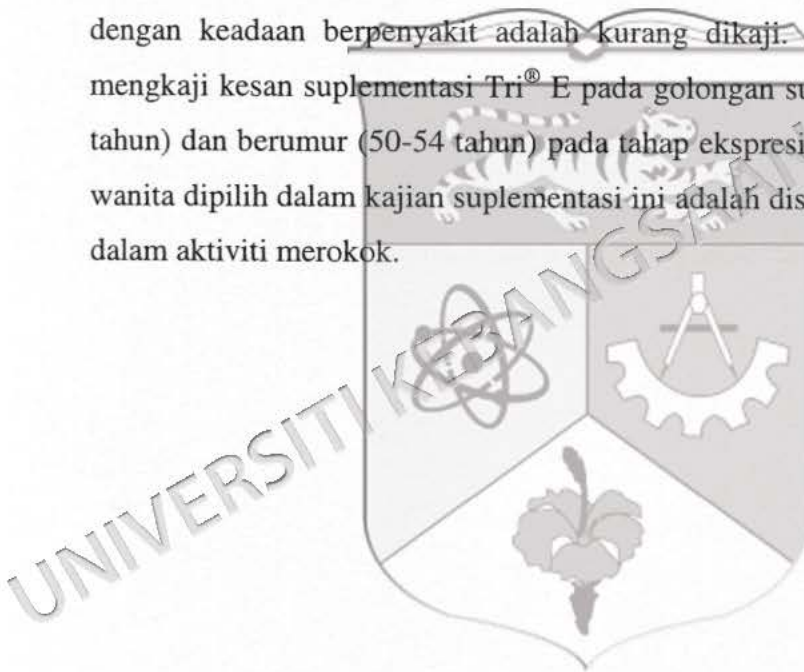
Tapak jalan utama diregulasi vitamin E adalah respon inflamasi (Han et al. 2006; Lin et al. 2007; Vasu et al. 2007). Faktor transkripsi NF- κ B mengawal ekspresi gen yang terlibat dalam inflamasi dan proliferasi (Ginn-pease et al. 1998; Kumar et al. 2004). Pengaktifan isyarat NF- κ B telah dikenalpasti berlaku pada *in situ* plak arteriosklerosis manusia (Brand et al. 1996). Antara gen utama yang terlibat dalam proses arteriosklerosis dan juga diregulasi oleh NF- κ B termasuk TNF, IL1, GCSF, MCP1, c-myc, ICAM1 dan VCAM1 (Collins & Cybulski 2001). Rawatan sel Jurkat-T dengan tokoferol asetat ataupun α -tokoferol susinat dapat merencatkan pengaktifan tapak jalan NF- κ B. Induksi sel endothelia dengan agen pengoksida LDL meningkatkan ekspresi gen dan protein seperti ICAM1 dan VCAM1 (Yoshida et al. 2000). Namun begitu, pre-rawatan dengan α -tokoferol mengurangkan ekspresi protein sel adhesi didapati bergantung kepada dos.

Kumpulan Angelo Azzi melaporkan fungsi α -tokoferol dalam isyarat sel selain daripada fungsi umum sebagai antioksidan (Boscoboinik et al. 1991). Proliferasi sel otot licin dan aktiviti protein kinase C (PKC) boleh direncat oleh α -tokoferol, tetapi β -tokoferol tiada kesan. Hasil kajian ini telah mencadangkan bahawa α -tokoferol bertindak pada PKC bebas daripada fungsi antioksidan disebabkan β -tokoferol juga memiliki ciri antioksidan yang lebih kurang sama. Perencatan PKC oleh α -tokoferol adalah berkaitan dengan pengaktifan PP2A yang defosforilasi PKC dan seterusnya menghalang aktivitiya (Ricciarelli et al. 1998). α -Tokoferol asetat dilaporkan boleh menurunkan produk PGE₂ melalui kawalan aktiviti COX (Wu et al. 2001). Namun begitu, α -tokoferol asetat ini tiada kesan pada ekspresi mRNA dan protein menunjukkan aktiviti post-translasi pada enzim COX. Jiang et al (2000) pula mendapati γ -tokoferol merencat COX-2 aktiviti pada sel makrofaj RAW264.7 yang diinduksi LPS dan sel epithelia manusia A549 diaruh IL1 β .

Pada peringkat protein pula, α -tokoferol dikatakan mengawal ekspresi protein yang terlibat dalam metabolisme lipoprotein. Aldred et al (2006) menjalankan kajian suplementasi α -tokoferol pada subjek sihat dengan dos 134 atau 368 mg sehari

ataupun plasebo selama 28 hari. Aplikasi teknologi spektrometer jisim dan pemblotan Western mendapati Apo A1 protein mengalami peningkatan yang signifikan bergantung kepada masa dan dos ($p < 0.01$ selepas 28 hari suplementasi dengan 268 mg α -tokoferol sehari). Data ini menunjukkan masa dan dos memainkan peranan penting dalam kajian suplementasi vitamin E dalam pengawalan ekspresi plasma protein subjek manusia.

Kesan suplementasi vitamin E adalah berlainan pada setiap individu sihat yang berbeza umur (Chin et al. 2008; Meydani 2004). Hal ini mungkin disebabkan status biologi individu muda dan berumur yang berbeza. Kesan suplementasi tokotrienol selain daripada tokoferol pada sel sistem imun subjek manusia sihat berbanding dengan keadaan berpenyakit adalah kurang dikaji. Oleh itu, kajian ini bertujuan mengkaji kesan suplementasi Tri[®] E pada golongan subjek wanita sihat muda (30-34 tahun) dan berumur (50-54 tahun) pada tahap ekspresi gen dan protein. Hanya subjek wanita dipilih dalam kajian suplementasi ini adalah disebabkan mereka kurang terlibat dalam aktiviti merokok.



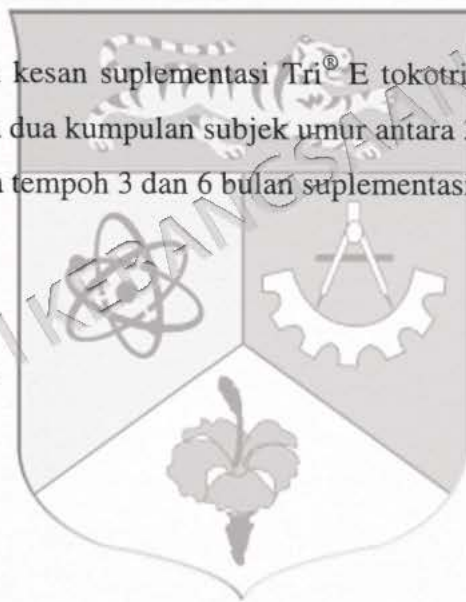
1.2 OBJEKTIF KAJIAN

1.2.1 Objektif Umum

Mengkaji kesan suplementasi Tri[®] E tokotrienol ke atas ekspresi gen dan protein di kalangan dua kumpulan subjek manusia berbeza umur.

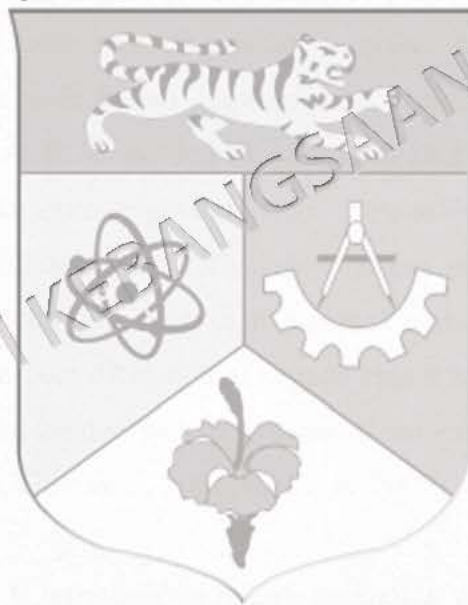
1.2.2 Objektif Khusus

- a) Menentukan kesan suplementasi Tri[®] E tokotrienol terhadap ekspresi gen pada sel PBMC dua kumpulan subjek umur antara 30-34 dan 50-54 tahun masing-masing pada tempoh 3 dan 6 bulan suplementasi.
- b) Menentukan kesan suplementasi Tri[®] E tokotrienol terhadap ekspresi protein pada plasma dua kumpulan subjek umur antara 30-34 dan 50-54 tahun masing-masing pada tempoh 3 dan 6 bulan suplementasi.



1.3 HIPOTESIS KAJIAN

- i. Suplementasi Tri[®] E tokotrienol menurunkan pengekspresan gen dan protein berkaitan dengan apoptosis dan inflamasi di kalangan kumpulan subjek muda dan berumur.
- ii. Suplementasi Tri[®] E tokotrienol meningkatkan pengekspresan gen dan protein berkaitan dengan antioksidan dan anti-apoptosis di kalangan kumpulan subjek muda dan berumur.
- iii. Tempoh suplementasi Tri[®] E tokotrienol yang panjang iaitu 6 bulan memberikan perlindungan yang lebih ketara dibandingkan dengan masa 3 bulan di kalangan golongan subjek muda dan berumur.



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